Claims

We claim:

1. A method for elevating the plasma level of high density lipoprotein (HDL) in a mammal, said method comprising administering to said mammal an HDL-elevating, therapeutically-effective amount of an LXRβ selective agonist.

2. The method of Claim 1 further comprising administering to said mammal an additional active agent selected from the group consisting of an antihyperlipidemic agent; a plasma HDL-raising agent; an antihypercholesterolemic agent; a cholesterol biosynthesis inhibitor; an acyl-coenzyme A: a cholesterol acyltransferase inhibitor; probucol; nicotinic acid and the salts thereof; niacinamide; a cholesterol absorption inhibitor; a bile acid sequestrant anion exchange resin; a low density lipoprotein receptor inducer; clofibrate, fenofibrate, gemfibrizol; vitamin B_6 and the pharmaceutically acceptable salts thereof; vitamin B_{12}; an anti-oxidant vitamin; a *beta*-blocker; an angiotensin II antagonist; an angiotensin converting enzyme inhibitor; a platelet aggregation inhibitor; a platelet aggregation inhibitor; a fibrinogen receptor antagonist; aspirin; a sulfonylurea; a biguanide, a thiazolidinedione; an insulin sensitizer; a dehydroepiandrosterone; an antiglucocorticoid; a TNFα inhibitor; an α-glucosidase inhibitor; pramlintide; an insulin secretogogue; insulin; phenylpropanolamine, phentermine, diethylpropion, mazindol; fenfluramine; dexfenfluramine; phentiramine; a β_3 adrenoceptor agonist agent; sibutramine; a gastrointestinal lipase inhibitor; a leptin; neuropeptide Y; enterostatin; cholecytokinin; bombesin; amylin; a histamine H_3 receptor; a dopamine D_2 receptor; melanocyte stimulating hormone; corticotrophin releasing factor; galanin; and gamma amino butyric acid (GABA).

3. A method for elevating the plasma level of high density lipoprotein (HDL) in a mammal, without elevating the plasma level of triglycerides, said method comprising administering to said mammal an HDL-elevating, therapeutically-effective amount of an LXRβ selective agonist.

4. A method of decreasing the absorption of dietary cholesterol in the intestine of a mammal, said method comprising administering to said mammal an absorption-decreasing, therapeutically-effective amount of an LXRβ selective agonist.

5. A method of elevating HDL-associated gene expression in a cell, said method comprising administering an LXRβ selective agonist to said cell.

6. The method of Claim 5 wherein the gene is encoded by a protein or polypeptide selected from the group consisting of ABCA1, ABCG1, CYP7A, ApoE, lipoprotein lipase, and a proinflammatory gene.

7. A method of decreasing the plasma level of low density lipoprotein (LDL) in a mammal, said method comprising administering to said mammal an LDL-decreasing, therapeutically-effective amount of an LXRβ selective agonist.

8. A method of decreasing the plasma level of low-density lipoprotein (LDL) in a mammal, without elevating the plasma level of triglycerides, said method comprising administering to said mammal an LDL-decreasing, therapeutically-effective amount of an LXRβ selective agonist.

9. A method of lowering the plasma level of low-density lipoprotein (LDL) in a mammal by increasing the conversion of cholesterol to bile acids, said method comprising administering a cholesterol-converting, therapeutically-effective amount of an LXRβ selective agonist.

10. A method of identifying an LXRβ selective agonist comprising:

a) selecting a candidate compound;

b) testing the candidate compound in a cell-based or biochemical assay that measures the LXRα and LXRβ agonist activity of the compound; and

c) identifying those candidate compounds which are LXRβ selective agonists as those compounds whose potency is lower for LXRβ as compared to LXRα; and/or whose efficacy is higher for LXRβ as compared to LXRα.

11. A method of identifying an LXRβ selective agonist comprising:

a) selecting a candidate compound;

b) contacting the candidate compound with a cell expressing LXRβ only and a first reporter gene containing DNA sequences to which LXRβ binds; and also contacting the candidate compound with a cell expressing LXRα only and a second reporter gene containing DNA sequences to which LXRα binds;

c) determining if the candidate is an LXRβ agonist and/or an LXRα agonist by examining the ability of the compound to induce transcription of the reporter gene under control of LXRβ and LXRα; and

d) identifying those candidate compounds which are LXRβ selective agonists as those compounds whose potency is lower for LXRβ as compared to LXRα; and/or whose efficacy is higher for LXRβ as compared to LXRα.

12. The method of Claim 10 wherein the LXRβ selective agonist is also an LXRα antagonist.

13. A method for treating a metabolic disease in a mammal, said method comprising administering to said mammal a therapeutically-effective amount of an LXRβ selective agonist.

14. The method of Claim 13 wherein said metabolic disease is selected from the group consisting of cardiovascular disease, such as atherosclerosis, diabetes, obesity, gallstone disease, syndrome X, hypertension, hypercholesterolemia, cholesterol absorption or transport disease, HDL deficiencies, and hyperlipidemia.

15. The method of Claim 14 wherein the disease is atherosclerosis.

16. The method of Claim 13 further comprising administering to said mammal an additional active agent selected from the group consisting of an antihyperlipidemic agent; a plasma HDL-raising agent; antihypercholesterolemic agent; a cholesterol biosynthesis inhibitor; an acyl-coenzyme A: a cholesterol acyltransferase inhibitor; probucol; nicotinic acid and the salts thereof; niacinamide; a cholesterol absorption inhibitor; a bile acid sequestrant anion exchange resin; a low density lipoprotein receptor inducer; clofibrate, fenofibrate, gemfibrizol; vitamin B_6 and the pharmaceutically acceptable salts thereof; vitamin B_{12}; an anti-oxidant vitamin; a beta-blocker; an angiotensin II antagonist; an angiotensin converting enzyme inhibitor; a platelet aggregation inhibitor; a platelet aggregation inhibitor; a fibrinogen receptor antagonist; aspirin; a sulfonylurea; a biguanide, a thiazolidinedione; an insulin sensitizer; a dehydroepiandrosterone; an antiglucocorticoid; a TNFα inhibitor; an α-glucosidase inhibitor; pramlintide; an insulin secretogogue; insulin; phenylpropanolamine, phentermine, diethylpropion, mazindol; fenfluramine; dexfenfluramine; phentiramine; a β_3 adrenoceptor agonist agent; sibutramine; a gastrointestinal lipase inhibitor; a leptin; neuropeptide Y; enterostatin; cholecytokinin; bombesin; amylin; a histamine H_3 receptor; a dopamine D_2 receptor; melanocyte stimulating hormone; corticotrophin releasing factor; galanin; and gamma amino butyric acid (GABA).

17. A method of preventing the onset of, reducing the risk of developing, or the risk of recurrence, a metabolic disease in a mammal, said method comprising administering to said mammal a therapeutically-effective amount of an LXRβ selective agonist.

18. The method of Claim 17 wherein said metabolic disease is selected from the group consisting of cardiovascular disease, such as atherosclerosis, diabetes, obesity, gallstone disease, syndrome X, hypertension, hypercholesterolemia, cholesterol absorption or transport disease, HDL deficiencies, and hyperlipidemia.

19. The method of Claim 18 wherein the disease is atherosclerosis.

20. A method for decreasing hyperglycemia and insulin resistance or associated cardiovascular complications arising from hyperglycemia and insulin resistance in a mammal,

said method comprising administering to said mammal, a therapeutically-effective amount of an LXR agonist.

21. A method for treating type II diabetes in a mammal, said method comprising administering to said mammal a therapeutically-effective amount of an LXR agonist.

22. A method for treating type II diabetes in a mammal and reducing the cardiovascular complications of type II diabetes, said method comprising administering to said mammal a therapeutically-effective amount of an LXR agonist.

23. The method of claim 22 further comprising administering an additional active agent selected from the group consisting of a sulfonylurea; a biguanide, a thiazolidinedione; an insulin sensitizer; a dehydroepiandrosterone; an antiglucocorticoid; a TNFα inhibitor; an α-glucosidase inhibitor; pramlintide; an insulin secretogogue; and insulin.

24. A method for treating obesity in a mammal, said method comprising administering to said mammal a therapeutically-effective amount of an LXRα selective antagonist.

25. A method for treating the complications of obesity in a mammal including type II diabetes, cardiovascular disease, hyperlipidemia, and hypertension, said method comprising administering to said mammal a therapeutically-effective amount of an LXRα selective antagonist.

26. The method of claim 25 further comprising administering an additional active agent selected from the group consisting of phenylpropanolamine, phentermine, diethylpropion, mazindol; fenfluramine; dexfenfluramine; phentiramine; a β_3 adrenoceptor agonist agent; sibutramine; a gastrointestinal lipase inhibitor; a leptin; neuropeptide Y; enterostatin; cholecytokinin; bombesin; amylin; a histamine H_3 receptor; a dopamine D_2 receptor; melanocyte

stimulating hormone; corticotrophin releasing factor; galanin; and gamma amino butyric acid (GABA).

27. A method of identifying an LXRα selective antagonist comprising:

a) selecting a candidate compound;

b) testing the candidate compound in a cell-based or biochemical assay that measures LXRα and LXRβ antagonist activity of the compound; and

c) identifying those candidate compounds which are LXRα selective antagonists as those compounds whose potency is lower for LXRα as compared to LXRβ; and/or whose efficacy as an antagonist is higher for LXRα as compared to LXRβ.

28. A method of identifying an LXRα selective antagonist comprising:

a) selecting a candidate compound;

b) contacting the candidate compound with a cell expressing LXRα only and a first reporter gene containing DNA sequences to which LXRα binds; and also contacting the candidate compound with a cell expressing LXRβ only and a second reporter gene containing DNA sequences to which LXRβ binds; and treating both sets of cells with LXR pan-agonist to induce transcription of the reporter gene;

c) determining if the candidate is an LXRα antagonist and/or an LXRβ antagonist by examining the ability of the compound to inhibit the pan-agonist induced transcription of the reporter gene under control of LXRα and LXRβ; and

d) identifying those candidate compounds which are LXRα selective antagonists as those compounds whose potency is lower for LXRα as compared to LXRβ; and/or whose efficacy as an antagonist is higher for LXRα as compared to LXRβ.